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NOTES ON THE PHARMACOLOGY OF BISMUTH, WITH REFERENCE TO ITS EMPLOYMENT IN THE THERAPY OF SYPHILIS

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THE use of bismuth as a substitute for mercury in the treatment of syphilis is growing rapidly. It may not, perhaps, be so powerful as mercury in equivalent dosage, but it is undoubtedly more convenient to use. Its effect (both therapeutic and toxic) is similar to that of mercury,¹ and, generally, the same can be said of its absorption, distribution in the body and elimination. To produce the same effect, somewhat larger doses of bismuth than of mercury are required, and possibly the therapeutic effect of bismuth may be slightly less than that of a strong mercurial treatment, but bismuth has the advantage that it is tolerated much better.

The principal objection to its use, from a practical point of view, is that it may give rise to the formation of a typical blue line at the margins of the gums. As a rule, this does not cause the patient any discomfort, but the discoloration is very obvious, and it is inevitable that sooner or later the general public will learn the meaning of this blue line, with the consequence that the patient bearing it will be branded almost as effectually as if the letter S had been stamped on his forehead.

Sometimes, when preparations are used which are absorbed slowly, the bismuth line is seen to develop and increase in strength after the administration of the bismuth has been stopped for some time. Since the discoloration persists for months, and cannot be removed by artificial means, its prevention requires care in the choice of the preparation and in its dosage.

As to choice of compound, the desiderata of a bismuth preparation are :

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(1) That it shall be absorbed fairly quickly, so that the therapeutic effect may be prompt and so that absorption may terminate quickly after stoppage of the administration on the appearance of warning signs of intoxication.

(2) That it shall be absorbed regularly, so that we may approach the threshold of maximum saturation of the organism without the risk of a sudden and unexpected serious intoxication, owing to the sudden influx into the organism of a large amount of the metal from the site of inoculation.

(3) That its injection shall not cause the patient more discomfort than he can reasonably tolerate.

The regular and slow saturation of the body with bismuth is necessary, because—as in the case of mercury—the effect is probably of an indirect character. It does not kill the spirochaetes directly, but, in some way which is not yet clear to us, it seems to stimulate the spirochaeticidal power of the tissues. For these reasons it is very important to understand clearly the facts about absorption and elimination (the two are almost identical) of the different preparations.

ABSORPTION AND ELIMINATION OF DIFFERENT PREPARATIONS OF BISMUTH

The absorption and elimination of bismuth might be learnt from careful clinical observations on a long series of patients. But direct examination of the curve of elimination of the metal bismuth after the injection of different preparations will afford us information which is quite as direct and reliable, since, as has been shown with mercury,² there is general agreement that, in regard to a given preparation, it is only the content and curve of absorption of the metallic bismuth which affect its therapeutic properties. The curve of absorption can be studied directly only in animals³; in patients our observations are necessarily limited to that of elimination. Elimination takes place partly through the urine (two-thirds) and partly through the faeces (one-third). The proportion eliminated through these channels remains fairly constant, so that, for purposes of comparison, our examination can be limited to the urine, which is much easier to work with than the faeces.

A number of patients were treated with different com-

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pounds of bismuth, and the absorption of these compared by estimations of the amounts of bismuth excreted through the urine. Since, as already mentioned, this is very approximately two-thirds of the total amount excreted, an addition of 50 per cent., representing that excreted through the fæces, provides the totals of the bismuth excreted. Formerly it was not easy to estimate small quantities of bismuth in organic tissues or fluids, but Hevesy's new method ⁴ has made this task much

TABLE I.—EXCRETION OF BISMUTH AFTER ADMINISTRATION OF DIFFERENT COMPOUNDS IN OILY SUSPENSIONS.

(To permit of a direct comparison of the different columns, the amounts of bismuth eliminated daily in the urine have been reduced to percentages of the total injected quantity of metallic Bi in each preparation.)

	HYDROXIDE OF Bi (50 mg. Bi injected). Elimination per diem.	IODOBISMUTHATE OF QUININE (90 mg. Bi injected). Elimination per diem.	TARTROBISMUTHATE OF SODIUM AND POTASSIUM (70 mg. Bi injected). Elimination per diem.
	Per cent.	Per cent.	Per cent.
1 . . .	0·32	0·00	2·19
2 . . .	0·52	1·60	5·26
3 . . .	0·36	1·38	3·38
4 . . .	0·40	1·27	2·51
5 . . .	0·40	1·27	1·80
6 . . .	0·54	1·13	1·34
7 . . .	0·62	0·87	1·22
8 . . .	0·54	1·38	1·10
9 . . .	0·60	1·21	0·79
10 . . .	0·66	0·66	0·81
11 . . .	0·96	0·98	0·38
12 . . .	0·50	1·33	0·49
13 . . .	0·74	1·36	0·44
14 . . .	0·42	1·13	0·49
Total	7·58 = 3·79 mg. Bi	15·57	22·20 = 15·54 mg. Bi
15 . . .	—	1·37	—
16 . . .	—	1·57	—
17 . . .	—	0·74	—
18 . . .	—	0·74	—
Total	—	19·99 = 17·99 mg. Bi	—

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easier. I employed this method in a previous series of experiments on rabbits,⁵ and adopted it for the present estimations. The preparations of bismuth administered to the patients fell into three of the principal groups of the innumerable bismuth compounds now on the market, being (1) bismuth hydroxide (Bi content about 80 per cent.), (2) vijochin, or iodobismuthate of quinine (Bi content about 20 per cent.), and (3) tartrobismuthate of potassium and sodium (Bi content about 64 per cent.). A detailed account of the experiments will be published later in *Annales de Dermatologie et de Syphiligraphie*; the space here permits me to give only a few examples. These, however, are representative of the total results.

The preparations were administered in oil and in watery suspension or solution respectively, and I will deal first with the oily suspensions. These have the great advantage of being almost painless, but, unfortunately, this advantage is obtained, as one might expect, at the cost of very slow absorption.

It will be seen clearly from the above table that, when administered in oily suspensions, hydroxide of bismuth is absorbed slowly. This is in accordance with its simple and rather solid construction. The iodobismuthate of quinine is absorbed about twice as quickly as the hydroxide. This compound is also in other respects less resistant than the first. The tartrobismuthate is absorbed about three times as quickly as the hydroxide. This is easily explained by the fact that it is soluble not only in water, but also in serum. The method used does not permit of researches of a longer duration than about three weeks, and I regret I can give no information concerning the elimination after that time. But I think it justifiable to say that the first two compounds, when administered in oily suspension, do not respond well to our demands. They are absorbed too slowly to give a strong immediate effect, unless given in very big doses, while the administration of a long series of injections of a slowly absorbed preparation, which thus accumulates in the tissues, is not ideal. Somewhat better is the tartrobismuthate, which is absorbed fairly well.

Here the following question presents itself: What is the reason of this slow absorption? As shown below, the vehicle of suspension proves to be the most important factor. Vast experience in mercurial therapy has shown

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that the metallic compounds suspended in vegetable oil are absorbed only slowly, owing to the very slow absorption of the oil itself. For this reason it seemed well justified to start a series of examinations with watery suspensions, and this was done with the following result. As tartro-bismuthate is soluble in water, the suspension quickly changes into a regular solution.

TABLE II.—EXCRETION OF BISMUTH AFTER ADMINISTRATION OF DIFFERENT COMPOUNDS IN WATERY SUSPENSIONS OR SOLUTIONS

	HYDROXIDE OF Bi (65 mg. Bi injected) Eliminated per diem.	IODOBISMUTHATE OF QUININE (90 mg. Bi injected) Eliminated per diem.	TARTROBISMUTHATE OF SODIUM AND POTASSIUM (50 mg. Bi injected) Eliminated per diem.
	Per cent.	Per cent.	Per cent.
1 . .	0·93	3·74	9·40
2 . .	2·18	5·93	12·40
3 . .	3·89	7·02	6·14
4 . .	4·03	5·27	3·62
5 . .	4·86	4·73	3·58
6 . .	4·81	3·72	3·02
7 . .	5·06	2·31	2·72
8 . .	4·18	2·20	1·80
9 . .	4·69	1·67	1·80
10 . .	3·29	1·40	2·04
11 . .	2·69	2·26	1·38
12 . .	2·49	1·31	1·12
13 . .	2·46	1·40	0·70
14 . .	2·00	1·04	0·54
Total	47·46 = 30·85 mg. Bi	44·00 = 39·67 mg. Bi	50·26 = 25·13 mg. Bi
15 . .	—	0·89	0·46
16 . .	—	1·35	0·98
17 . .	—	1·05	0·70
18 . .	—	0·45	0·54
19 . .	—	0·44	0·46
20 . .	—	0·32	0·46
21 . .	—	0·13	—
Total	. . .	48·63 = 43·77 mg. Bi	53·86 = 26·93 mg. Bi

A comparison of the results given in this series with those in Table I. leaves no doubt as to the importance of the vehicle of suspension. A watery suspension favours

a very quick absorption and elimination. During a fortnight about two-fifths to one-half of the bismuth is found in the urine. To this amount must be added about 25 per cent. of the injected quantity which is eliminated through the fæces (see above), while part of the injected metal is distributed in different parts of the body. Consequently we are entitled to consider that most of the bismuth contained in each of the three preparations injected was absorbed from the site of injection after fourteen days.

Comparing the rates of absorption of the three different preparations in watery suspension or solution, the differences are in the same order as in the case of the oily suspensions, but are somewhat less pronounced. The solution of tartrobismuthate is much more quickly absorbed than the suspensions, but this is only what would be expected.

A comparison of these results shows clearly that the watery suspensions or solutions must be preferred for practical use. They afford a more rapid and thus a more regular and reliable absorption than the oily ones. This fact permits us to regulate our scheme of dosage fairly finely, and to stop an approaching intoxication moderately quickly. After the injections are stopped the absorption from the dépôts will increase during only a short period, and thus we can avoid a strong blue line establishing itself in the gums.

Of the three different compounds examined here, I would prefer the hydroxide. The tartrobismuthate solution is rather painful in therapeutic doses, and its curve of absorption is more abrupt than desirable for practical use. The iodobismuthate is not practical, because its content of Bi is inconstant and is also very low, so that one has to administer about four times as much of the compound as of the hydroxide to obtain an equivalent therapeutic effect.

A purely watery suspension is not to be recommended for the use of the practitioner, because the suspension is very unstable, but the addition of a small amount of glycerine (only 10 per cent.) helps greatly to overcome this difficulty. The addition of glycerine makes it easy to retain the preparation in homogeneous suspension sufficiently long for practical purposes, a short energetic shaking only being necessary immediately before the syringe is filled and the injection is made.

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A SIMPLE METHOD OF PREPARING BISMUTH HYDROXIDE

In my hands the following suspension has proved very satisfactory. It contains 20 per cent. of hydroxide of bismuth and 10 per cent. glycerine. It is extraordinarily easy to prepare as follows: 12 grammes of the basic nitrate of bismuth are dissolved in dilute nitric acid. A surplus of ammonia is added, resulting in a fine precipitate of hydroxide of bismuth. This precipitate must be very carefully washed out, preferably under aspiration. Then 10 c.c. of glycerine and 40 c.c. of sterile water are added, and the suspension is ready for use.

I have tested the curve of elimination of this preparation and found the figures uniform with those of a purely watery suspension, thus:—

SUSPENSION OF HYDROXIDE OF BISMUTH (20 PER CENT.) IN WATER AND GLYCERINE. (65 mg. Bi injected.)

Daily Elimination in the Urine.

				Per cent.
1.	.	.	.	1.04
2.	.	.	.	4.09
3.	.	.	.	4.49
4.	.	.	.	2.60
5.	.	.	.	4.97
6.	.	.	.	3.96
7.	.	.	.	2.57
8.	.	.	.	3.56
9.	.	.	.	3.00
10.	.	.	.	1.76
11.	.	.	.	3.49
12.	.	.	.	3.34
13.	.	.	.	1.45
14.	.	.	.	1.85
Total				42.17 = 27.41 mg. Bi
15.	.	.	.	1.46
16.	.	.	.	1.42
17.	.	.	.	1.43
18.	.	.	.	0.90
19.	.	.	.	1.49
Total				48.87 = 31.77 mg. Bi

This preparation is very cheap, costing less than one halfpenny for a dose of 0.2 gramme. It is very easy to handle, and it is fairly well tolerated by the patients when

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given in the upper part of the buttock, most injections being painless, or practically so. In a certain proportion of cases, however, the injections are followed by slight stiffness of the hip, or slight pain. Some few patients will complain of moderate pain, but it is only in exceptional cases (2 to 3 per cent.) that the pain is so severe as to interfere with sleep, and until now I have been asked by only one or two patients to stop the injections, of which I have given more than a thousand.

As to dosage, I think that about 20 cg., viz., 1 c.c., of the suspension given once a week will prove to be the right single dose for an average man. A big man will perhaps require 30 cg., and a small woman only 10 to 15 cg. After five to seven injections a tiny blue line developing round the teeth will mark the approaching saturation of the body. A full course ought to consist of eight to ten injections. In a few cases the line will appear after only three or four injections. In such cases one must be careful, because a strong discoloration, once established, will remain for several months. With very sensitive patients it may be advisable to divide the single weekly dose into two of 10 cg. each. I have never seen this dose give any pain worth mentioning. The clinical effect of the remedy has been perfectly satisfactory, and I have seen large eruptions disappear after only two to three injections.

REFERENCES

- (1) *Biochem. Jl.*, vol. 18, p. 683.
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- (3) *Biochem. Jl.*, *loc. cit.*
- (4) *Compt. rend. de l'Acad. des Sciences*, 1924, T. 178, p. 1324; T. 179, p. 291.
- (5) *Biochem. Jl.*, *loc. cit.*